REMARKS

Status of the Claims

Claims 1-5, 7-10, 12-16 and 60 have been rejected. Claims 6-8, 11, 17-59 have been canceled without prejudice or disclaimer. Applicant reserves the right to pursue the subject matter of claims 6-8, 11, and 17-59 in a continuation or divisional application. Claims 61-70 have been added. Claims 1-5, 9-10, 12-16 and 60-70 are pending.

Applicants note that newly submitted claims 69 and 70 recite various methods of detection which were subjected to a species restriction in the Restriction Requirement of October 6, 2003. In view of the response to Restriction filed on February 6, 2003, the species drawn only to "mobilization" is presently under examination.

Amendment to the Claims

Claim 1 was amended to clarify the claimed invention. Specifically, step (e) of claim 1 was removed. Step (d) of claim 1 was also removed. Support for this amendment can be found, for example, on page 4, lines 9-12 which recite that the helper function can be supplied by the host cell. Step (d) of claim 1 was amended to clarify that the recombinant encodes a functional gag and a functional pol polypeptide. Support for this amendment can be found, for example, on page 31, lines 15-18 and page 7, lines 20-25 of the specification.

Support for newly added claim 61 which recites "a retroviral genetic recombinant having gag and pol functions" can be found on page 7, lines 20-24 and on page 10, lines 22-34; support for "providing a cell suspected of having said recombinant" can be found, for example, on page 5, lines 20-27 of the specification; support for "determining the presence of said recombinant having the gag and pol functions" can be found, for example, on page 6, lines 12-25.

Support for newly submitted claim 62 which recites the genetic recombinant comprises functional gag polypeptide and a functional pol polypeptide can be found, for example, on page 31, lines 15-18 and page 7, lines 20-25 of the specification.

Support for newly submitted claim 63 which recites that the cell comprises "at least one helper function" can be found, for example, on page 4, line 9-12 of the specification. Support for newly submitted claim 64 which recites that the "helper function comprises envelope or a

psuedotype thereof" can be found, for example, on page 8, lines 1-5 of the specification. Support for newly submitted claims 65, 66, and 67 which recites a the trans-viral vector system is a trans-lenti vector system can be found, for example, on page 37, lines 20-30 of the specification. Support for newly submitted claim 68 which recites that the method is used to evaluate the risk of producing a replication-competent retrovirus from a retroviral-based vector can be found, for example in original claim 59. Support for newly submitted claims 69 and 70 can be found, for example, in original claim 4.

No new matter has been added by way of these amendments.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-5, 9-10, 12-16 and 60 were rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. This rejection is respectfully traversed.

Claim 1 was rejected for being indefinite for not reciting the structure of the trans-viral vector system. The Examiner's attention is drawn to page 25, line 19 and Example 8 (pages 37 and 38) which explain that the trans-viral system is "based on a gag-pro (not a gag-pol) packaging construct that promotes a "disarming" of lentiviral recombinants by eliminating the production of functional reverse transcriptase (RT) and integrase (IN) from the traditional packaging vector." In addition, U.S. Applications and scientific literature publications which discuss this trans-viral vector system are also disclosed. See, page 37, lines 15-20 of the specification. Consequently, the specification does provide a description of a trans-viral vector. In summary, both the specification and the prior art provide sufficient guidance for one of skill in the art to determine the scope of the term "trans-viral vector." Accordingly, the rejection of claim 1 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claim 1 and its respective dependant claims 3-5, 9-10, 12-16, and 60 were also rejected for being indefinite for not reciting "what the viral particle comprises." Applicants assume the Examiner is objecting to step (c) of claim 1 which recites "members of said viral particle population may comprise said recombinant." The Examiner's attention is drawn to page 4, lines 28-30 of the specification, where a "recombinant" is defined as a species of a retrovirus that has undergone a nucleic acid recombination event. In view of the description of a trans-viral vector

system and the definition of the term "recombinant", the metes and bound of the claim is clear. To expedite prosecution, however, claim 1 has been amended to remove the phrase at issue. Accordingly, the rejection of claim 1 under 35 U.S.C. §112, second paragraph, and its respective dependant claims 3-5, 9-10, 12-16, and 60, should be withdrawn.

Claim 5 was rejected for being indefinite for the use of the term "one or more genetic element." This rejection is respectfully traversed. Claim 5 recites that the recombinant comprises "one or more genetic elements selected from the group consisting of retroviral cis-acting sequences and retroviral coding sequences, wherein said genetic elements facilitate reverse transcription and integration." First, the claim itself recites that the genetic elements are a retroviral cis-acting sequence or a regroviral coding sequence. Second, claim 5 further has a functional descirption of the genetic elements (i.e., "the genetic elements facilitate reverse transcription and integration"). Third, examples of such elements were known in the art and are provided in the specification. See, for example, page 12, lines 29-30 and page 13, lines 1-7 of the specification which states that,

> In addition, multiple "cis-acting" (noncoding) elements are generally thought to be necessary, e.g., long terminal repeat (LTR) sequences, a retroviral packaging signal (Ψ), a polyadenylation signal, a promoter or promoters for expressing the genes (usually within the 5' LTR sequence), a transfer RNA binding site (PBS), a polypurine tract (PPT) that facilitates initiation of first and second-strand DNA synthesis, a repeated R region that is required for transfer of DNA synthesis between templates; and short, partially inverted repeats that are located at the termini of the viral LTRs and that are required for integration.

And fourth, assays to measure for reverse transcriptase activity and integration were known in the art. Consequently, the specification does provide a standard for measuring the recited activity.

In summary, both the specification and the prior art provide sufficient guidance for one of skill in the art to determine the scope of the phrase "one or more genetic elements selected from the group consisting of retroviral cis-acting sequences and retroviral coding sequences, wherein

said genetic elements facilitate reverse transcription and integration." Accordingly, the rejection of claim 5 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claim 9 was rejected for being indefinate for the term "capable of." The Examiner asserts that the "capablity of a compound or composition to perform some function is merely a statement of a latent characteristic of the compound or composition and the language carries no patentable weight." The rejection is resepctfully traversed.

Claim 9 recites that the "recombinant is capable of mobilizing a nucleic acid sequence." The Examiner's attention is drawn to MPEP 2173.05(g) that discusses the acceptability of functional language. The Examiner is respectfully requested to consider *In re Barr*, 170 USPQ 33 (CCPA 1971) which held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought.

In the instant case, the claim at issue employs language that further characterizes the function of the recombinant as "capable of mobilizing a nucleic acid sequence." To determine the acceptability of claim language, one must determine if one of skill in the art would understand what is claimed, in view of the specification. The functional language appearing in claim 9 is clear, and assays to detect this activity can be found, for example, in Example 6 of the specification. Accordingly, the Examiner is respectfully requested to withdraw the rejection.

Claims 9 and 10 were rejected for being indefinite for the term "a nucleic acid sequence" (claim 9) and "a retroviral nucleic acid sequence" (claim 10). This rejection is respectfully traversed. The terms at issue are routine in the art. Claims 9 and 10 recite that the recombinant is "capable of mobilizing" a nucleic acid sequence. As explained on page 18-23 of the specification mobilizing" refers to "the process, method or ability of replicating a recombinant and/or other provirus...and transmitting it to another cell." Moreover, page 34 provides an example of assaying for the mobilization of a nucleic acid sequence. Any sequence, if employed in the vector appropriately, can be monitored for mobilization. Accordingly, the metes and

bounds of the terms appearing in claims 9 and 10 are clear, and the Examiner is respectfully requested to withdraw the rejection.

Claim 4 was rejected for the term "mobilization." The Examiner asserts that the specification "does not give the definition of mobilization." While an explicit definition in the specification is not required to render a term definite, Applicants draw the Examiner's attention to page 15, lines 18-23 of the specification which defines the term "mobilizing" as the process, method or ability of replicating a recombinant and/or other provirus...and transmitting it to another cell. Applicants submit that the claim term is clear, and the Examiner is respectfully requested to withdraw the rejection of claim 4 under 35 U.S.C. §112, second paragraph.

The Rejection of the Claims Under 35 U.S.C. §102 Should Be Withdrawn

Claims 1, 3, 4, 9, 10, 12-13 and 15 were rejected under 35 U.S.C. §102 in view of Miller *et al.* (1991) *J. Virol. 65*:2220-2224. This rejection is respectfully traversed.

Miller *et al.* constructs retrovirus packaging cells expressing the MoMLV gag-pol protein and the GaLV envelope protein. These cells can produce high-titer retroviral vectors. The teachings of Miller *et al.* do not anticipate amended claim 1 or newly submitted claims 61-70.

Independent claims 1 and 61 recite a "trans-viral vector." As explained on page 25, line 19 and in Example 8, a trans-viral vector is based on a gag-pro construct not a gag-pol packaging construct. Miller *et al.* teaches only the use of a gag-pol construct and therefore does not teach a trans-viral vector as recited in the instant claims. See, for example, page 2221, Figure 1 of Miller *et al.* which provides an illustration of the viral vector employed. The construct, called pLGPS, contains a gag-pol coding sequence. Accordingly, claims 1, 61, and 64 are not anticipated by Miller *et al.*

In addition, claims 1, 63 and 64 recite that the cell line in which the viral particle is being introduced comprises a helper function. As defined on page 5, lines 10-15 of the specification, a helper function is used to facilitate propagation of the recombinant when the recombinant is one that is incapable or inefficient at replicating, packaging, and/or infecting by itself. Examples of helper functions include but are not limited to the retroviral env gene product and pseudotypes

thereof and/or the retroviral tat and rev gene products. Contrary to the assertions by the Examiner, Miller *et al.* does not employ a helper function as defined by the claims of the present invention. The Examiner states that Miller *et al.* provides helper functions by providing the envelope polypeptide or the dhfr and hpt selectable markers. *However, these steps are simply the production of a packaging cell line that will produce the desired retroviral particle.*

Any recombinants formed by Miller *et al.* are not detected by the use of helper functions. In fact, the Examiner's attention is drawn to page 2221, column 1, last sentence of first paragraph of Miller *et al.* which states "helper virus was measured using the $S^+L^-$ assay." For the Examiner's convenience the $S^+L^-$ assay is discussed in Miller *et al.* (1985) *Molecular and Cellular Biology* 5:431-437, which is provided herewith in Appendix A. As outlined on page 432, column 1 of Miller *et al.* (1985), the $S^+L^-$ assay requires incubating viral particle produced from a packaging cell line with cells susceptible to viral infection. Only replication competent virus will be able to replicate in the cells and result in foci formation. Accordingly, the $S^+L^-$ assay does not employ "helper functions" as recited in claims 1, 63, and 64.

For the reasons discussed above claims 1-5, 9-10, 12-16 and 60, as well as, newly submitted claims 61-70 are not anticipated by Miller *et al.* (1991), and the Examiner is respectfully requested to withdraw the rejection.

Claims 1, 3, 4, 9, 10, 12-13, and 15 were rejected under 35 U.S.C. §102(b) as being anticipated by Naldini *et al.* (1996) *Science* 272:263-267. This rejection is respectfully traversed.

Naldini *et al.* teaches an HIV-based viral vector system comprising a three-plasmid expression system. The system comprises a packaging construct (expressing gag-pol), an envelope construct, and a transducing construct. The teachings of Naldini *et al.* do not anticipate claims 1, 3, 4, 9, 10, 12-13, 15 or newly added claims 61-70.

Independent claims 1 and 61 recite a "trans-viral vector." Naldini *et al.* teaches only the use of a gag-pol construct and therefore does not teach a trans-viral vector as recited in the instant claims. See, for example, page 263, Figure 1 which provides an illustration of the viral

vector employed by Naldini *et al.* The packaging construct contains a gag-pol coding sequence. Accordingly, independent claims 1 and 61 are not anticipated by Naldini *et al.*

In addition, independent claims 1, 63 and 64 recite that the cell line in which the viral particle is being introduced comprises a helper function. Contrary to the assertions by the Examiner, Naldini *et al.* does not employ a helper function as defined by the claims of the present invention. The Examiner asserts that Naldini *et al.* provides helper functions by providing the marker genes and envelope polypeptide. *However, these steps are simply the production of a packaging cell line that will produce the desired retroviral particle.* Any recombinants formed by Naldini *et al.* are not detected by the use of helper functions. In fact, the Examiner's attention is drawn to page 264, column 2, second sentence of first paragraph which states "the potential transfer of packaging functions from producer to target cells was assayed by testing for the production of the tat and gag gene products in vector transduced cells." Such assays do not employ the use of helper functions as defined by the present invention, and moreover, the assay by Naldini *et al.* will not allow one to determine the presence of a recombinant having a functional gag and a functional pol polypeptide as recited in claims 1 and 62.

For the reasons discussed above claims 1-5, 9-10, 12-16 and 60, as well as, newly submitted claims 61-70 are not anticipated by Naldini *et al.*, and the Examiner is respectfully requested to withdraw the rejection.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 1-5, 9-10, 12-16 and 60 were rejected under 35 U.S.C. §103(a) as being unpatentable in view of Kafri *et al.* (1999) *J. Virol. 73*:576-584. Claim 14 was rejected under 35 U.S.C. §103 as being unpatentable in view of Kafri *et al.* and Morgenstern *et al.* (1990) *Nucleic Acid Research 18*:3587-3596. This rejection is respectfully traversed.

Kafri *et al.* teaches the use of a three-plasmid lentiviral vector system. See, for example, page 579, column 1, first paragraph, which discusses the viral vector employed. Specifically, the system used a packaging cell line (SODk0) which contains the first construct comprising a transfer construct. A second construct containing envelope and a third construct containing gag-

pol are introduced into the SODk0 cell line to form the viral particle. Morgenstern *et al.* employs a retroviral vector and was cited by the Examiner because of its use of the selection markers in the viral particles.

A *prima facie* case of obviousness requires the references to teach each element of the claimed invention. The cited references to do not satisfy this requirement. Kafri *et al.* employs three assays: tat transfer, HIV gag transfer and marker rescue. See, page 577. The tat transfer assay employed by Kafri *et al.* comprise the following steps: 1) replication incompetent lentivirus was produced from SODk1 packaging cells; 2) the presence of helper virus in the viral stock was assayed by infecting HeLaP4.2 cell line which is characterized by an integrated lacZ reporter gene driven off the HIV LTR; and, 3) assaying for GFP expression. See, Kafri *et al.* page 577, column 1, paragraphs 1 and 6. Kafri *et al.* assays only for the presence of tat. Claim 1 and newly submitted claim 62 recite that the method allows one to determine the presence of recombinants having a functional gag and a functional pol polypeptide. The tat assay employed by Kafri *et al.* does not necessarily result in the detection of a functional gag and a functional pol as recited in claims 1 and 62. In addition, the tat assay employed by Kafri *et al.* does not employ a helper function as recited in claims 1 and 63 and further does not teach a trans-viral vector, as recited in claim 1 and newly submitted claim 61.

The HIV gag transfer assay employed by Kafri *et al.* measured p24gag in conditioned media obtained from vector transduced cells. The vector stock discussed above was allowed to infect the HeLaP4.2 cells. Following passage in culture, the concentration of p24gag in conditioned media was determined. See, Kafri *et al.* page 577, column 1, paragraph 7. Again, unlike claim 1 and 62 of the present invention, the HIV gag transfer assay taught by Kafri *et al.* detects an antigen of gag and therefore does not allow one to determine the presence of recombinants having a functional gag or a functional pol polypeptide. In addition, the gag transfer assay does not employ a helper function as recited in claims 1 and 63 and further does not employ a trans-viral vector as recited in claims 1 and 61.

In the marker rescue assay disclosed in Kafri *et al.*, HeLaP4.2 cells were transduced with a HR'CMV GFP lentivirus. The transduced cells were cultured and the media was harvested. 293T cells were incubated in the presence of the media, and cells having GFP were detected.

See, Kafri *et al.* page 577, column 2, paragraph 1. The marker rescue assay disclosed by Kafri *et al.* also does not employ a trans-viral vector or a helper function as recited in claims 1 and 61.

Morgenstern *et al.* also does not provide the elements missing from the Kafri *et al.* reference. As each element recited in the claims has not been taught or suggested by the cited references, a *prima facie* case of obviousness under 35 U.S.C. §103 has not been established, and the Examiner is respectfully requested to withdraw the rejection and not apply the rejection to the newly submitted claims.

## CONCLUSIONS

The Examiner is respectfully requested to withdraw the rejections and allow claims 1-5, 9-10, 12-16, and 60-70. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

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RTA01/2160236v1